(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 434 405 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **90313945.9**

(22) Date of filing: **19.12.90**

(51) Int. Cl.5: **C07D 471/04**, A61K 31/44, //(C07D471/04,235:00,221:00)

(30) Priority: **21.12.89 US 454556**
24.07.90 US 557247

(43) Date of publication of application:
26.06.91 Bulletin 91/26

(84) Designated Contracting States:
AT BE CH DE DK ES FR GR IT LI LU NL SE

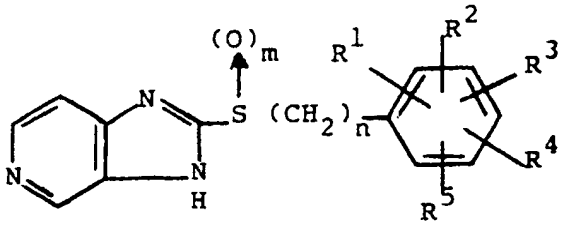
(71) Applicant: **AMERICAN HOME PRODUCTS CORPORATION**
685, Third Avenue
New York, New York 10017(US)

(72) Inventor: **Santilli, Arthur Attilio**
1737 Sue Ellen Drive
Havertown, Pennsylvania(US)
Inventor: **Scotese, Anthony Carmen**
240 Beidler Road
King of Prussia, Pennsylvania(US)
Inventor: **Strike, Donald Peter**
445 Ivan Avenue
St. Davids, Pennsylvania(US)

(74) Representative: **Wileman, David Francis Dr. et al**
c/o Wyeth Laboratories Huntercombe Lane South
Taplow Maidenhead Berkshire SL6 OPH(GB)

(54) Imidazo[4,5-c]pyridines as antiosteoporotic agents.

(57) The invention describes compounds of formula (I)



or tautomer thereof, wherein R^1, R^2, R^3, R^4 and R^5 are independently selected from hydrogen, lower alkyl containing 1 to 6 carbon atoms, hydroxy, lower alkyloxy containing 1 to 6 carbon atoms, halogen, trifluoromethyl, trifluoromethoxy, nitro, cyano, phenoxy, benzyloxy, acetamido $-S(O)_p-CH_3$ or any two adjacent groups are joined to form methylenedioxy; m is 0 to 2; n is 1 to 3; p is 0 to 2, and pharmaceutically acceptable salts and hydrates thereof which are useful as antiosteoporotic agents

EP 0 434 405 A1

IMIDAZO[4.5-C]PYRIDINES AS ANTIOSTEOPOROTIC AGENTS

This invention relates to 2-imidazo[4,5-c]pyridines, to processes for their preparation, to pharmaceutical compositions containing said 2-substituted-imidazo[4,5-c]pyridines and to the use of said 2-substituted-imidazo[4,5-c]pyridines for modifying the balance between bone production and bone resorption in 8 host animal, including man.

BACKGROUNDOFTHEINVENTION

Osteoporosis is a skeletal disorder which is evidenced by an increase in fracture incidence resulting from a decrease in bone density. In fact, both the bone mineral (calcium phosphate called "hydroxyapatite") and the bone matrix (major protein called "collagen") are lost. This condition may begin to occur in humans as early as age 30. In general, the process is more rapid in postmenopausal women than in men. However, after age 80 there is no sex difference in the incidence of osteoporosis. In the course of 10 to 20 years of bone loss there may be symptoms of back pain and X-ray evidence of deformation of the spine. At older ages, the brittleness of the bones becomes evident by the ease with which the proximal femur ("hip") fractures. Osteoporosis is the most common cause of fractures in people over age 45.

Although the cause of osteoporosis is poorly understood, it is believed that there is an imbalance between bone production and bone resorption (bone breakdown). Bone remains a dynamic tissue throughout the life of an animal. That is, new bone is continuously being formed and old bone is continuously being resorbed. However, in animals suffering from an osteoporotic condition, net bone resorption exceeds bone formation.

A survey indicates that in the United States there may be fifteen to twenty million people afflicted with osteoporosis [W.A. Peck (Chairman), NIH Osteoporosis Consensus Conference, J. Am. Med. Assoc., 10, 252:799-802(1984)]. Various types of osteoporosis are designated according to special conditions believed to be causative: senile (aging); post-menopausal (female loss of estrogenesis); disuse (chronic immobilization); steroid (long term steroid treatment as in arthritis); hypercalcemia of malignancy. Osteoporosis may also be manifested in dental problems since the mandible appears to lose mass more rapidly than any other bone. Thus, periodontal disease involving a loosening of the adult teeth may be an early sign of osteoporosis.

The mechanism of bone loss is at present poorly understood. Moreover, the present methods of treatment are generally unsatisfactory. These include anabolic agents, various drugs containing phosphorous, Vitamin D, calcium salts, fluorides and calcitonin.

Estrogen replacement therapy has been the therapy of choice for osteoporosis in post-menopausal women.

Physical therapy is another method currently used to treat osteoporosis since immobilization can cause osteoporosis at any age. Thus, many physicians believe that exercise and physical therapy can prevent the progression of the disease in elderly patients. However, physical therapy can be harmful for patients with fractures and, moreover, overstrenuous exercise can cause fractures in patients with severe osteoporosis.

Other treatments include the administration of a fluoride salt such as sodium fluoride which has been shown to promote bone growth clinically, apparently by stimulating collagen synthesis. However, a serious side effect is poorly calcified, irregular bone growth. Another treatment involves infusion of calcium and Vitamin D to counteract the deficiency of calcium or impaired absorption of calcium which is symptomatic in some elderly patients. There is, however, no evidence that a higher intake of calcium will prevent osteoporosis or increase bone mass in adults.

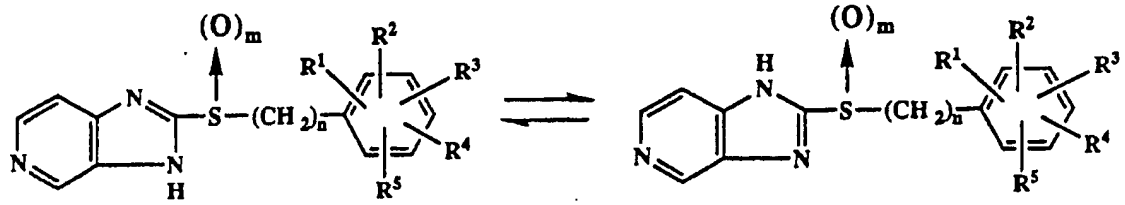
The most promising therapeutic approach to the treatment of osteoporosis is the administration of agents which have been designed to modify the balance between the rate of bone production and the rate of bone resorption in such a manner that the ratio of the former to the latter is increased, resulting in no net bone loss. After the previously occurred bone losses have been restored, a steady state is reached where the rate of bone production and rate of bone resorption are equal. Such a modification may be effected by stimulating the physiological mechanism of bone deposition, i.e., bone formation, or by retarding the mechanism of bone resorption, or both. Drugs presently in use or in the experimental stages for accomplishing these purposes include phosphonates, calcitonin and mithramycin. However, all of these drugs suffer serious drawbacks.

Mithramycin, an antibiotic, has anti-tumor activity together with hypocalcemic activity, causing a reduction of serum calcium which in turn is believed to be indicative of a decrease in the relative rate of bone resorption - i.e., bone resorption relative to bone production. Side effects, however, include renal and

hepatic toxicity as well as nausea. Likewise, the organic phosphonates have side effects which include extraskeletal calcification, hypotension and renal failure. Calcitonin presents an immunological problem because it is commonly derived from a non-human source. Thus, none of the foregoing agents are at present suitable for use alone in the treatment of osteoporosis.

The closest prior art is Japanese Patent J6 3146-883-A and International Patent Application WO 89/03829; WO 89/03830 and WO 89/03833.

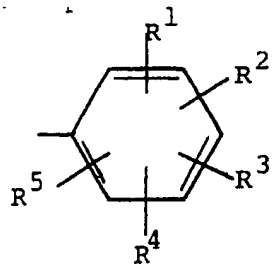
This invention provides 2-substituted-imidazo[4,5-c]pyridine derivatives useful in inhibiting bone resorption and having the formula (I) or its tautomer having the formula (I')



(I) (I')

wherein R^1, R^2, R^3, R^4, and R^5 are independently selected from hydrogen, lower alkyl containing 1 to 6 carbon atoms, hydroxy, lower alkyloxy containing 1 to 6 carbon atoms, halogen, trifluoromethyl, trifluoromethoxy, nitro, cyano, phenoxy, benzyloxy acetamido, $-S(O)_p-CH_3$ or any two adjacent groups are joined to form methylenedioxy; m is 0 to 2; n is 1 to 3; p is 0 to 2, and the pharmaceutically acceptable salts and hydrates thereof.

Examples of alkyl when a group or or part of a group are methyl, ethyl, propyl, butyl. Examples of halogen are chlorine, bromine and fluorine. Examples of R^1, R^2, R^3, R^4, and R^5 are independently hydrogen, hydroxy, methoxy, ethoxy, propoxy, butoxy, fluorine, chlorine, bromine, methyl, ethyl, propyl, butyl, t-butyl, CF_3, benzyloxy, NO_2, CN, phenoxy, or acetamido or any adjacent pair of R^{1-5} is methylenedioxy . More particularly examples of



are phenyl, 3-methoxyphenyl, 3-benzyloxyphenyl, 3-methylphenyl, 3-nitrophenyl, 3-trifluoromethylphenyl, 3-ethoxyphenyl, 3-hydroxyphenyl, 3,4-dichlorophenyl, 2-chloro-6-fluorophenyl; 2,4,6-trimethylphenyl; 4-bromo-2-fluorophenyl; 3,4,5-trimethoxyphenyl, pentafluorophenyl, 3,4-difluorophenyl, 4-t-butylphenyl, 2-cyanophenyl, 2-fluorophenyl, 2-methoxyphenyl, 3,5-dimethoxyphenyl, 4-methoxy-3-methylphenyl and 4-acetamidophenyl.

Examples of m are 0 and 1. Examples of n are 1 and 2.

Preferred compounds of the present invention are those of formula (I) wherein R^1, R^2, R^3, R^4 and R^5 are independently selected from hydrogen, hydroxy, methoxy, fluorine, chlorine, methyl, trifluoromethyl, benzyloxy or any two adjacent groups are joined to form methylenedioxy; m is 0 to 2; n is 1 to 2, and the pharmaceutically acceptable salts thereof.

The most preferred compounds of the present invention are designated

2-[[(3-methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5c]pyridine;

2-[[(3-methoxyphenyl)methyl]thio]-1H-imidazo[4,5]pyridine;

2-[[(3-methoxyphenyl)methyl]sulfonyl]-1H-imidazo[4,5-c]pyridine;

2-[[(3,4-dichlorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;

2-[[[3-(trifluoromethyl)phenyl]methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;

2-[[(2-chloro-6-fluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;

2-[[(phenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[(2-phenylethyl)sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-methoxyphenyl)ethyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(2,4,6-trimethylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(4-bromo-2-fluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[[3-(phenylmethoxy)phenyl]methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(6-chloro-1,3-benzodioxol-5-yl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(4-methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3,4,5-trimethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3,4-difluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(pentafluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-methylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(4-t-butylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(1H-imidazo[4,5-c]pyridin-2-yl)sulfinyl]methyl]benzonitrile;
2-[[(2-fluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(2-methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3,5-dimethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-phenoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-nitrophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(4-methoxy-3-methylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-ethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
N-[4-[(1H-imidazo[4,5-c]pyridin-2-ylsulfinyl)methyl]phenyl]acetamide;
[S-(+)]-2-[[3-methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
[R-(-)]-2-[[(3-methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
3-[[(1H-imidazo[4,5-c]pyridin-2-yl)sulfinyl]methyl]-phenol; and the pharmaceutically acceptable salts thereof.

The sulfoxides of this invention possess an asymmetric sulfur atom and thus are made as racemic mixtures. It is to be understood that the definition of the sulfoxides of Formula (I) and (I') encompasses all possible stereoisomers, R and S enantiomers, tautomers and mixtures thereof which possess the activity discussed below. In particular, it encompasses racemic modifications and any optical isomers which possess the indicated activity.

Optical isomers may be obtained in pure form by standard separation techniques. For example a racemic mixture may be converted to a mixture of optically active diastereoisomers by reaction with a single enantiomer of a 'resolving agent' for example by salt formation or formation of a covalent bond). The resulting mixture of optically active diastereoisomers may be separated by standard techniques(e.g crystallisation or chromatography) and individual optically active diastereoisomers then treated to remove the 'resolving agent' thereby releasing the single enantiomer of the compound of the invention. Chiral chromatography (using a chiral support, eluent or ion pairing agent) may also be used to separate enantiomeric mixtures directly.

Stereospecific synthesis using optically active starting materials and/or chiral reagent catalyst and/or solvents may also be employed to prepare a particular enantiomer.

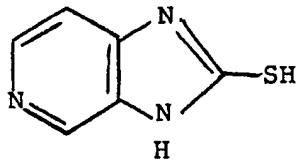
For example where the compound of formula I is prepared by an addition process creating an optical centre then carrying out the reaction using a chiral catalyst or agent or in a chiral environment can give the product as a single enantiomer.

The pharmaceutically acceptable salts of the compounds of this invention are prepared directly by neutralization of the free base. These physiologically acceptable salts may be formed with strong organic or inorganic acids, such as hydrochloric, hydrobromic, phosphoric, sulfuric, sulfamic, nitric, methylsulfonic, maleic, fumaric, naphthalenesulfonic acid and the like.

This invention also provides processes for the production of 2-substituted-imidazo[4,5-c]pyridines.

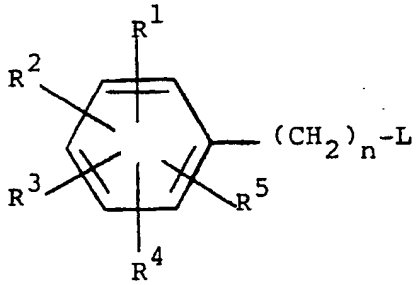
Accordingly this invention provides a process for preparing a compound of formula I or tautomer thereof as defined above or a pharmaceutically acceptable salt thereof which comprises one of the following:

a) reacting a compound of formula



(II)

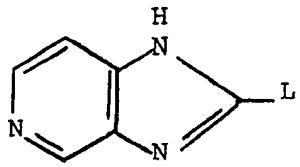
or tautomer thereof, or an alkali metal salt thereof e.g sodium, potassium or lithium salt, with a compound of formula



(III)

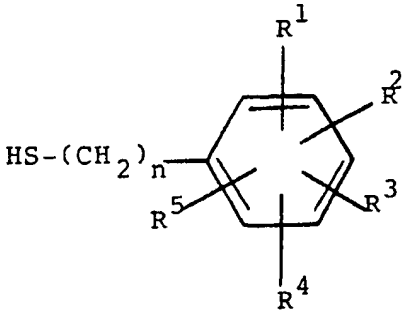
wherein n, R^1 , R^2, R^3, R^4 and R^5 are as defined and L is a leaving group e.g a halogen such as chlorine, bromine or iodine or an organic sulphonyloxy group such as aryl or alkyl-sulphonyloxy, e.g tosyloxy to give a compound of formula I or tautomer thereof wherein m is zero, or

b) reacting a compound of formula



(IV)

or tautomer thereof, wherein L is a leaving group as described above with a compound of formula



(V)

or an alkali metal salt thereof wherein n, R^1 , R^2 , R^3, R^4 and R^5 are as defined in above to give a compound of formula I or a tautomer thereof wherein m is zero, or

c) oxidising a compound of formula I or a tautomer thereof to give a corresponding compound of formula I or tautomer thereof wherein m is 1 or 2, or

d) dealkylating a compound of formula I or tautomer thereof wherein any one of R^1, R^2, R^3, R^4 and R^5 is

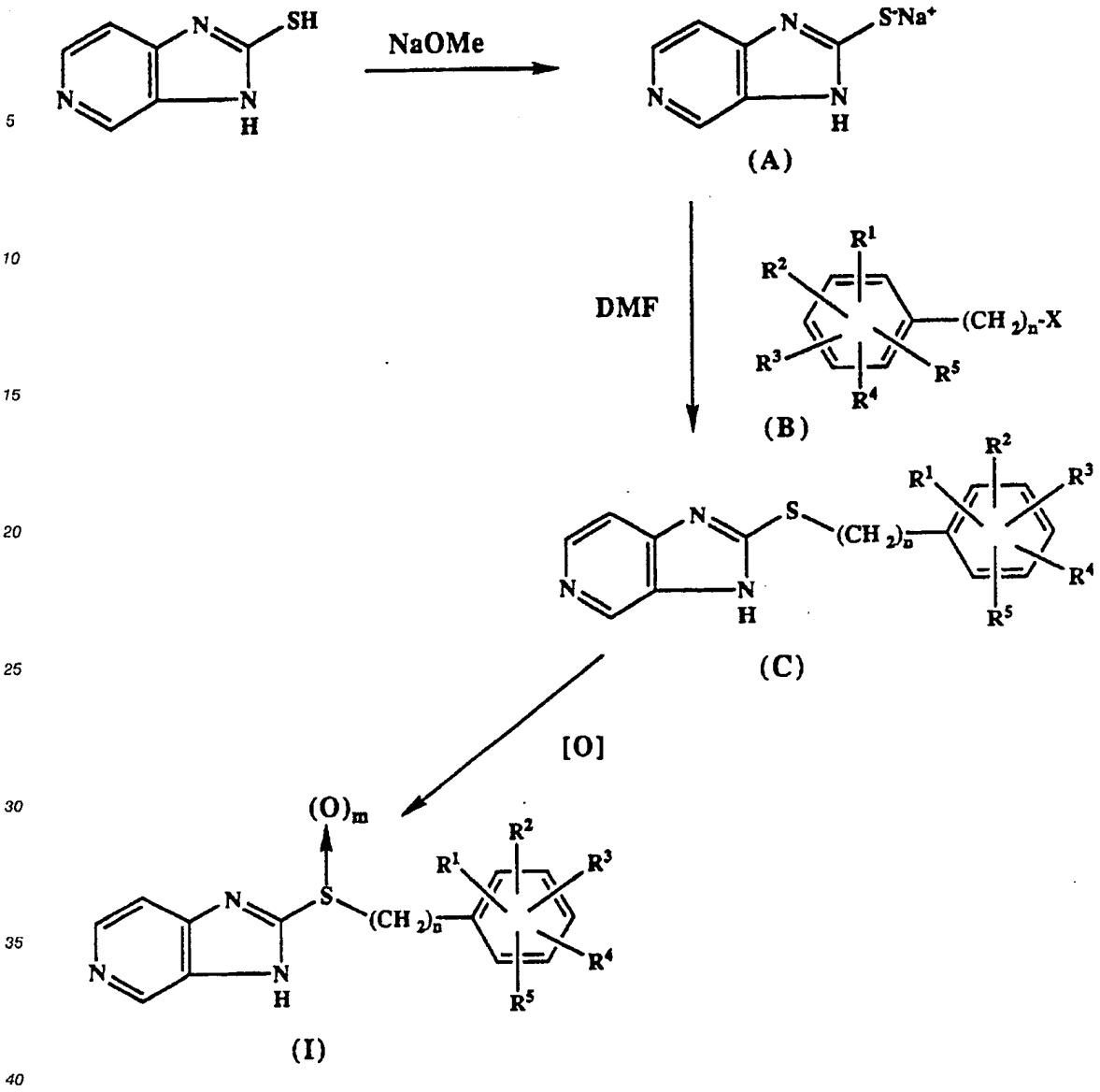
lower alkyloxy to give a compound of formula I or tautomer thereof wherein any one of R^1, R^2, R^3, R^4 and R^5 is hydroxy, or

e) acidifying a basic compound of formula I or tautomer thereof to give an acid addition salt or neutralizing an acid addition salt to give the free base of formula I or tautomer thereof.

With regard to processes a) and b) the reaction may be conveniently carried out in the presence of base and a polar inert solvent. If the compounds of formula II and (V) are reacted in the presence of an alkali metal base then the alkali metal salt may be formed initially and this is then reacted with the compound of formula (III) or (IV).

The oxidation process (c) may be carried out by any suitable means for forming a sulfoxide from a thioether (see Kharasch, Organic Sulphur Compounds, Pergamon Press, New York,1961 Volume 1, pages 157-159) for example by using a peracid or peroxide. Examples of such acids are perbenzoic, m-chloroperbenzoic or peracetic acid. Hydrogen peroxide may also be used. Oxidation using two equivalents yields the sulfonyl compounds where m = 2. Where it is desired to prepare a sulfoxide of formula I enantioselectively then oxidation using a homochiral oxygen transfer agent, e.g. a Davis sulfonyloxaziridine or a Sharpless procedure (e.g a hydroperoxide tartrate combination in the presence of a titanium catalyst) may be used. A preferred route to compounds of formula I and tautomers thereof is shown below:-

REACTION SCHEME



wherein R^1, R^2, R^3, R^4, R^5, m and n are as defined above and X is Cl, Br, I or tosyl.

The compounds of this invention are generally prepared sequentially by first forming the sodium salt of 2-mercaptoimidazo[4,5-c]pyridine (A) with sodium methoxide. Treatment of (A) in DMF with an equivalent of a suitably substituted alkylating agent (B), affords the corresponding sulfide derivative (C). Finally, oxidation of (C) with an equivalent of an oxidizing agent such as selenium dioxide/hydrogen peroxide or m-chloroperoxybenzoic acid at reduced temperature affords the desired sulfoxide (I).

It is also another object of this invention to provide a method whereby a host animal, including man, suffering from osteoporosis is treated in order to modify the balance between the rates of bone deposition and bone resorption in said host animal whereby the ratio of the latter to the former is reduced.

Still another object of this invention is to provide a process for the treatment of a host animal in order to prevent the deterioration of existing healthy bone tissues in said host animal. It is possible that these agents could also be of utility in the treatment of hypercalcemia of malignancy, Paget's disease, hyperparathyroidism, immobilization, glucocorticoid-induced osteopenia, and the arthritides.

It is a further object of this invention to provide a process for the treatment of periodontal disease.

This invention also provides a pharmaceutical composition comprising a compound of formula I or a tautomer thereof, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of formula (I) of this invention are used alone or in combination with pharmacologically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard medical practice. For example, they are administered orally in the form of capsules, tablets, suspensions or solutions or by oral topical administration or they may be injected parenterally. Capsules and tablets are the preferred mode of administration. For parenteral administration they can be used in the form of a sterile solution containing other solutes, for example enough saline or glucose to make the solution isotonic.

The capsule and tablet compositions contain the active ingredient in admixture with non-toxic pharmaceutical excipients known to be suitable in the manufacture of capsules and tablets. Suitable pharmaceutical excipients are, for example, starch, milk sugar, certain types of clay and so forth. The tablets can be uncoated or they can be coated by known techniques so as to delay disintegration and absorption in the gastro-intestinal tract and thereby provide a sustained action over a longer period.

The aqueous suspensions of the compounds of formula (I) contain the active ingredient in admixture with one or more non-toxic pharmaceutical excipients known to be suitable in the manufacture of aqueous suspensions. Suitable excipients are, for example, methylcellulose, sodium alginate, gum acacia, lecithin and so forth. The aqueous suspensions can also contain one or more preservatives, one or more coloring agents, one or more flavoring agents and one or more sweetening agents.

Non-aqueous suspensions can be formulated by suspending the active ingredient in a vegetable oil for example, arachis oil, olive oil, sesame oil, or coconut oil, or in mineral oil, for example liquid paraffin, and the suspension may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. These compositions can also contain a sweetening agent, flavoring agent and antioxidant.

The dosage of the compounds of formula (I) will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular host as well as the age, weight and condition of the host under treatment, as well as with the nature and extent of the symptoms. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects. For example, the effective amount of the compounds for oral administration can usually range from about 200 mg to 1200 mg/day in single or divided doses although, as aforementioned, variations will occur. However, a dosage level that is in the range of from about 500 mg to 900 mg/day in single or divided doses is employed most desirably for oral administration in order to achieve effective results.

The following examples are provided to illustrate the methods of preparation and testing of the compounds of the present invention. These examples are not meant to be considered, in any way, as limitations of the breadth and scope of the present invention. The temperatures expressed in these examples are in degrees centigrade.

EXAMPLE1

2-Mercapto-1H-imidazo[4.5-c]pyridine

A mixture of 25 g (0.23 mol) of 3,4-diaminopyridine in 750 mL of ethanol containing 50 mL (63.2 g, 0.83 mol) of carbon disulfide was heated under reflux for 5 hours. The reaction mixture was allowed to cool to room temperature and the beige precipitate which had formed was collected by filtration and allowed to air dry overnight. The product amounted to 33.5 g,m.p.>320 ° C.
Ref. G.B. Barlin, J. Chem. Soc (B)285(1966)

EXAMPLE2

2-[[(3-Methoxyphenyl)methyl]thio]-1H-imidazo[4.5-c]pyridine

To a solution containing 3.45 g (0.15 g atom) of sodium dissolved in 800 mL of methanol was added 22.65 g (0.15 mol) of 2-mercapto-1H-imidazo[4,5-c]pyridine. The reaction mixture was stirred for 1/2 hour at room temperature. The solvent was removed in a rotary evaporator and to the residue was added 465 mL of DMF. 3-Methoxybenzyl chloride (23.49 g, 0.15 mol) was then added dropwise and the reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into approximately 1800 mL of water and allowed to cool for several hours in an ice bath. The product was removed by filtration and amounted to 28.3 g. Recrystallization from ethyl acetate gave 18.6 g of product. An analytical sample (m.p.

133-136° C) was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{13}N_3OS$:	C, 61.97; H, 4.83; N, 15.49
Found:	C, 61.91; H, 4.81; N, 15.48.

EXAMPLE3

2-[[(3-Methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4.5-c]pyridine

2-[[(3-Methoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine (9.88 g, 0.036 mol) was dissolved in 130 mL of methanol by heating. An oxidizing solution was prepared by dissolving 4.0g (0.036 mol) of selenium dioxide in 150 mL of methanol with heating followed by the addition of 4.07 g (0.036 mol) of 30% hydrogen peroxide and 2.5 mL of water. The oxidizing solution was cooled to room temperature and was added dropwise to the sulfide solution. The reaction mixture was stirred overnight. The precipitate which had formed was collected on a filter and rinsed with petroleum ether giving 4.68 g of product. An analytical sample (m.p. 176-179° C) was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{13}N_3O_2S$:	C, 58.42; H, 4.56; N, 14.62
Found:	C, 58.47; H, 4.53; N, 14.62.

EXAMPLE4

2-[[3-Methoxyphenyl)methyl]sulfonyl]-1H-imidazo[4.5-c]pyridine

To a 2.35 g (0.009 mol) solution of 2-[[(3-methoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine in 100 mL of methylene chloride was added, dropwise, and while stirring, a solution containing 4.2 g (0.02 mol) of m-chloroperoxybenzoic acid in 200 mL of methylene chloride. The reaction mixture was stirred at room temperature for four days. The precipitate (1.52 g) which formed was collected and washed with 10% sodium bicarbonate solution. An analytical sample (m.p. 200-203° C) was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{13}N_3O_3S$:	C, 55.43; H, 4.32; N, 13.85
Found:	C, 55.66; H, 4.33; N, 13.98.

EXAMPLE5

2-[[(3.4-Dichlorophenyl)methyl]thio]-1H-imidazo[4.5-c]pyridine

To a solution of 0.34 g (0.015 g atom) of sodium in 70 mL of methanol was added 2.0 g (0.013 mol) of 2-mercapto-1H-imidazo[4,5c]pyridine. The reaction mixture was stirred at room temperature for 20 minutes and was evaporated to dryness in a rotary evaporator. To the residue was added 40 mL of DMF followed by the dropwise addition of 2.54 g (0.013 mol) of α,3,4-trichlorotoluene in 3 mL of DMF. The reaction mixture was stirred overnight at room temperature and was then poured into 400 mL of chilled water. The reaction mixture was extracted with chloroform (3x150 mL). The organic phases were combined and dried over magnesium sulfate. The solution was filtered and the Filtrate was evaporated to dryness in a rotary evaporator. There was obtained 2.66 g of product. An analytical sample (m.p. 190-193° C) was obtained by recrystallization from acetonitrile.

Anal. Calcd. for $C_{13}H_9Cl_2N_3S$:	C, 50.34; H, 2.92; N, 13.55
Found:	C, 50.41; H, 2.72; N, 13.46.

EXAMPLE6

2-[[(3.4-Dichlorophenyl)methyl]sulfinyl]-1H-imidazo[4.5-c]pyridine

[[(3,4-Dichlorophenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine (1.3 g, 0.0042 mol) was dissolved in 26 mL of methanol with heating. An oxidizing solution consisting of 0.48 g (0.0042 mol) of selenium dioxide and 0.48 g (0.0042 mol) of 30% hydrogen peroxide and 0.5 mL of water in 9 mL of methanol was added dropwise to the sulfide solution. The reaction solution was stirred at room temperature overnight. The product (1.66 g) was collected by filtration. An analytical sample, m.p. 198-201 °C, was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_9Cl_2N_3OS$:	C, 47.87; H, 2.78; N, 12.88
Found:	C, 47.67; H, 2.77; N, 12.66.

EXAMPLE7

2-[[[3-(Trifluoromethyl)phenyl]methyl]thio]-1H-imidazo[4.5-c]pyridine

To a solution of 0.15 g (0.0065 g atom) of sodium in 35 mL of methanol was added 1.0 g (0.0066 mol) of 2-mercapto-1H-imidazo[4,5-c]pyridine. After stirring for 15 minutes at room temperature, the methanol was removed in a rotary evaporator. The residue was dissolved in 20 mL of DMF and 1.28 g (0.0066 mol) of α'-chloro-α,α,α-trifluoro-m-xylene in 2 mL of DMF was added dropwise to the reaction solution. The reaction mixture was stirred at room temperature overnight and was then poured into 150 mL of ice water. The product which crystallized was collected and amounted to 1.61 g. An analytical sample (m.p. 148-150 °C) was obtained by recrystallization from acetonitrile.

Anal. Calcd. for $C_{14}H_{10}F_3N_3S$:	C, 54.36; H, 3.26; N, 13.59
Found:	C, 54.45; H, 3.21; N, 13.50.

EXAMPLE8

2-[[[3-(Trifluoromethyl)phenyl]methyl]-sulfinyl]-1H-imidazo[4.5-c]pyridine

2-[[[3-(Trifluoromethyl)phenyl]methyl]thio]-1H-imidazo[4,5-c]pyridine (0.91 g, 0.0029 mol) was dissolved in 10 mL of ethanol. An oxidizing solution was prepared by dissolving 0:32 g (0.0029 mol) of selenium dioxide in 17 mL of ethanol by heating and adding 0.33 g (0.0029 mol) of 30% hydrogen peroxide and 0.25 mL of water. The oxidizing solution was added dropwise to the sulfide solution and the reaction mixture was stirred overnight at room temperature. Water (20 mL) was added to the reaction mixture which was then extracted with chloroform (3x25 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated to dryness. The residue amounted to 0.65 g. Purification by HPLC gave a product which on recrystallization from ethanol had a m.p. 194-197 °C.

Anal. Calcd. for $C_{14}H_{10}F_3OS$:	C, 51.69; H, 3.10; N, 12.92
Found:	C, 51.95; H, 3.07; N, 12.81.

EXAMPLE9

2-[[(2-Chloro-6-fluorophenyl)methyl]thio]-1H-imidazo[4.5-c]pyridine

To a solution of 0.34 g (0.015 g atom) of sodium in 70 mL of ethanol was added 2.0 g (0.013 mol) of 2-mercapto-1H-imidazo[4,5-c]pyridine. After stirring at room temperature for 25 minutes, the reaction mixture was evaporated to dryness in a rotary evaporator. To the residue was added 40mL of DMF. To the resulting solution was added dropwise 2.33 g (0.013 mol) of 2- chloro-6-fluorobenzyl chloride in 3mL of DMF. The reaction mixture was stirred overnight at room temperature and was then poured into 400 mL of chilled water. The precipitate that formed was collected by Filtration and amounted to 3.11 g. An analytical sample (m.p. 224-226 °C) was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_9ClFN_3S$:	C, 53.15; H, 3.09; N, 14.30
Found:	C, 53.29; H, 3.30; N, 13.95.

EXAMPLE10

2-[[(2-Chloro-6-fluorophenyl)methyl]-sulfinyl]-1H-imidazo[4.5-c]pyridine

2-[[(2-Chloro-6-fluorophenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine (2.6 g, 0.0089 mol) was dissolved in 140 mL of methanol containing 20 mL of ethyl acetate. An oxidizing solution was prepared by heating 0.99 g (0.0089 mol) of selenium dioxide in 40 mL of methanol and adding 1.01 g (0.0089 mol) of 30% hydrogen peroxide and 0.65 mL of water. The oxidizing solution was added dropwise with stirring to the sulfide solution. The reaction mixture was stirred overnight at room temperature. Approximately 1/2 the solvent was removed in a rotary evaporator and the reaction mixture was chilled in ice. The resulting precipitate was collected and amounted to 1.08 g. An analytical sample, m.p. 180-183 °C, was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_9ClFN_3OS$:	C, 50.41; H, 2.93; N, 13.57
Found:	C, 50.45; H, 3.01; N, 13.26.

EXAMPLE11

2-[[(Phenyl)methyl]thio]-1H-imidazo[4.5-c]pyridine

To a solution of 1.26 g (0.055 g atom) of sodium in 300 mL of methanol was added 7.56 g (0.05 mol) of 2-mercapto-1H-imidazo[4,5-c]pyridine with stirring. After 20 minutes, the reaction mixture was evaporated to dryness in a rotary evaporator. Dimethyl formamide (200 mL) was added to the residue. To the resulting solution was added dropwise 6.33 g (0.05 mol) of benzylchloride. The reaction mixture was stirred for 5 hours at room temperature and was then poured into 1500 mL of water. The product was removed by filtration and amounted to 9.5 g, m.p. 175-177 °C. The product was triturated with hot ethyl acetate and refiltered. The product amounted to 8.11 g, m.p. 175-177 °C. A portion recrystallized from ethyl acetate gave the analytical sample (m.p. 175-177 °C).

Anal. Calcd. for $C_{13}H_{11}N_3S$:	C, 64.70; H, 4.59; N, 17.41
Found:	C, 64.55; H, 4.62; N, 17.12.

EXAMPLE12

2-[[(Phenyl)methyl]sulfinyl]-1H-imidazo-[4.5-c]pyridine

To a chilled (0-5° C) solution of 3.3 g (0.014 mol) of 2-[[(phenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine in 50 mL of chloroform and 5 mL of methanol was added dropwise a solution containing 2.78 g (0.014 mol) of m- chloroperoxybenzoic acid in 50 mL of chloroform. The reaction mixture was then stirred at room temperature for 45 minutes. Approximately one half of the chloroform was removed in a rotary evaporator and the reaction mixture was then poured into 200 mL of ether. The reaction mixture was cooled in ice. The precipitate that formed was collected and amounted to 1.78 g. The product was suspended in aqueous 10% sodium bicarbonate solution, filtered and was air dried overnight. The product amounted to 1.39 g. An analytical sample (m.p. 190-193° C) was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{11}N_3OS$:	C, 60.68; H, 4.31; N, 16.33
Found:	C, 60.39; H, 4.17; N, 16.47.

EXAMPLE13

2-[(2-Phenylethyl)thio]-1H-imidazo[4.5-c]pyridine

To a solution of 0.17 g (0.0074 g atom) of sodium in 35 mL of methanol was added 1.0 g (0.0066 mol) of 2-mercapto-1H-imidazo[4,5-c]pyridine. After stirring the reaction for 25 minutes at room temperature, the reaction mixture was evaporated to dryness in a rotary evaporator. To the residue was added 20 mL of DMF. To the resulting solution was added dropwise, 1.22 g (0.0066 mol) of 2-(bromoethyl)benzene in 3 mL of DMF. The reaction mixture was stirred overnight at room temperature and was then poured into 100 mL of chilled water. There was obtained 1.0 g of product. An analytical sample (m.p. 164-166° C) was prepared by recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{13}N_3S$:	C, 65.85; H, 5.13; N, 16.46
Found:	C, 66.04; H, 5.23; N, 16.06.

EXAMPLE14

2-[(2-Phenylethyl)sulfinyl]-1H-imidazo[4.5-c]pyridine

2-[(2-Phenylethyl)thio]-1H-imidazo[4,5-c]pyridine (2.4 g, 0.0094 mol) was dissolved in 120 mL of chloroform with heating. The reaction solution was cooled in an ice bath to 0-5° C. m-Chloroperoxybenzoic acid (1.91 g, 0.0094 mol) was added portionwise. The reaction mixture was then stirred at room temperature for 1 hour. 10% aqueous sodium bicarbonate was added and the organic layer was separated and dried over magnesium sulfate. After filtering, the filtrate was evaporated to half the volume in a rotary evaporator. Ether was added to the cloudy point and the reaction mixture was cooled in ice. The crystals that had formed amounted to 0.63 g. An analytical sample, m.p. 171-174° C, was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{13}N_3OS$:	C, 61.97; H, 4.83; N, 15.49
Found:	C, 61.73; H, 4.81; N, 15.09.

EXAMPLE15

3-Methoxyphenethanol,p-Toluenesulfonate

A solution of 18.82 g (0.099 mol) of p-tosylchloride in 80 mL of pyridine was added dropwise to a solution of 12.5 g (0.082 mol) of 3-methoxyphenethyl alcohol in 120 mL of pyridine at ice bath temperature. The reaction mixture was then allowed to stir at room temperature for 2 hours. The pyridine was removed in a rotary evaporator. Water (100 mL) was added to the residue. The aqueous solution was then extracted with chloroform (3x100 mL). The combined chloroform layers were dried over magnesium sulfate, filtered and the filtrate taken to dryness in a rotary evaporator. The residual oil was purified by HPLC and used directly in the next step.

EXAMPLE16

2-[[(3-Methoxyphenyl)ethyl]thio]-1H-imidazo[4.5-c]pyridine

To a solution of 0.81 g (0.035 g atom) of sodium in 170 mL of methanol was added 4.83 g (0.032 mol) of 2-mercapto-1H-imidazo[4,5-c]pyridine. After stirring for 25 minutes, the methanol was removed in a rotary evaporator and to the residue was added 100 mL of DMF. The residue dissolved after heating for a few minutes. The reaction mixture was allowed to cool to room temperature and 9.79 g (0.032 mol) of 3-methoxyphenethanol, p- toluenesulfonate ester in 5 mL of DMF was slowly added dropwise. The reaction mixture was allowed to stir at room temperature overnight and then was poured into 725 mL of chilled water. The reaction mixture was extracted with chloroform (3x200 mL). The combined organic phase was dried over magnesium sulfate, filtered and the filtrate was evaporated to dryness in a rotary evaporator. The crude product amounted to 12.6 g which was used directly in the next step.

EXAMPLE17

2-[[(3-Methoxyphenyl)ethyl]sulfinyl]-1H-imidazo[4.5-c]pyridine

2-[[(3-Methoxyphenyl)ethyl]thio]-1H-imidazo[4,5-c]pyridine (4.0 g, 0.014 mol) was dissolved in 60 mL of chloroform and cooled in an ice bath to 0-5° C. m-Chloroperoxybenzoic acid (3.13 g, 0.015 mol) was added in portions to the reaction mixture. After 45 minutes, 10% aqueous sodium bicarbonate solution was added. The organic layer was removed and dried over magnesium sulfate, filtered and evaporated to dryness in a rotary evaporator. The crude product (4.2 g) when subjected to HPLC gave 2.3 g of pure product, m.p. 125-128° C.

Anal. Calcd. for $C_{15}H_{15}N_3O_2S$:	C, 59.78; H, 5.02; N, 13.94
Found:	C, 59.47; H, 4.84; N, 13.71.

EXAMPLE18

2-[[(2,4,6-Trimethylphenyl)methyl]thio]-1H-imidazo[4.5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using α^2-chloroisodurene chloride, m.p. 150-153° C. (quarterhydrate)

Anal. Calcd. for $C_{16}H_{17}N_3S \cdot \frac{1}{4} H_2O$:	C, 66.75; H, 6.09; N, 14.59
Found:	C, 66.84; H, 5.97; N, 14.67.

EXAMPLE19

2-[[(2,4,6-Trimethylphenyl)methyl]sulfinyl]-1H-imidazo[4.5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 214-217° C.

Anal. Calcd. for $C_{16}H_{17}N_3OS$:	C, 64.14; H, 5.72; N, 14.03
Found:	C, 64.00; H, 5.66; N, 13.93.

EXAMPLE20

2-[[(4-Bromo-2-fluorophenyl)methyl]thio]-1H-imidazo[4.5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 4-bromo-2-fluorobenzyl chloride, m.p. 204-206° C.

Anal. Calcd. for $C_{13}H_9BrFN_3S$:	C, 46.17; H, 2.68; N, 12.42
Found:	C, 45.99; H, 2.81; N, 12.46.

EXAMPLE21

2-[[(4-Bromo-2-fluorophenyl)methyl]sulfinyl]-1H-imidazo[4.5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 208-212° C (dec.).

Anal. Calcd. for $C_{13}H_9BrFN_3OS$:	C, 44.08; H, 2.56; N, 11.86
Found:	C, 44.03; H, 2.59; N, 11.83.

EXAMPLE22

2-[[[3-Phenylmethoxy)phenyl]methyl]thio]-1H-imidazo[4.5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 3-benzyloxybenzyl chloride, m.p. 161-164° C.

Anal. Calcd. for $C_{20}H_{17}N_3OS$:	C, 69.14; H, 4.93; N, 12.09
Found:	C, 68.90; H, 4.93; N, 11.59.

EXAMPLE23

2-[[[3-(Phenylmethoxy)phenyl]methyl]sulfinyl]-1H-imidazo[4.5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 195-197° C (dec.).

Anal. Calcd. for $C_{20}H_{17}N_3O_2S$:	C, 66.09; H, 4.72; N, 11.56
Found:	C, 65.93; H, 4.62; N, 11.54.

EXAMPLE24

2-[[(6-Chloro-1,3-benzodioxol-5-yl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 6-chloropiperonyl chloride, m.p. 212-214° C.

Anal. Calcd. for $C_{14}H_{10}ClN_3O_2S$:	C, 52.59; H, 3.15; N, 13.14
Found:	C, 52.52; H, 3.10; N, 12.77.

EXAMPLE25

2-[[(2-Chloro-1,3-benzodioxol-5-yl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 210-213° C. (dec.).

Anal. Calcd. for $C_{14}H_{10}ClN_3O_3S$:	C, 50.08; H, 3.00; N, 12.51
Found:	C, 49.79; H, 2.94; N, 12.40.

EXAMPLE26

2-[[(4-Methoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 4-methoxybenzyl chloride, m.p. 160-161° C.

Anal. Calcd. for $C_{14}H_{13}N_3OS$:	C, 61.97; H, 4.83; N, 15.49
Found:	C, 62.00; H, 4.51; N, 15.22.

EXAMPLE27

2-[[(4-Methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-cl-pyridine

The synthesis of this compound as the one third hydrate proceeded in the same fashion as in Example 10.

Anal. Calcd. for $C_{14}H_{13}N_3O_2S \cdot 1/3\ H_2O$:	C, 57.32; H, 4.69; N, 14.32
Found:	C, 57.31; H, 4.47; N, 14.12.

EXAMPLE28

2-[[(3,4,5-Trimethoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11. The product was characterized as the hydrochloride salt.

Anal. Calcd. for $C_{16}H_{18}ClN_3O_3S$:	C, 52.24; H, 4.93; N, 11.42
Found:	C, 52.28; H, 4.92; N, 11.29.

EXAMPLE29

2-[[(3,4,5-Trimethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

A solution of 5.56 g (0.009 mol) of magnesium monoperphthalate hexahydrate in 30 mL of water was added to 4.95 g (0.015 mol) of 2-[[(3,4,5-trimethylphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine (free base) in 50 mL of ethanol. The stirred reaction mixture was heated to 50° C for 3 hours and then overnight at room temperature. An additional 1.86 g (0.003 mol) of the oxidant in 10 mL of water was added to the reaction mixture. The reaction mixture was heated for 1 hour at 50° C. An additional 30 mL of water was added and the reaction mixture was extracted with chloroform (3x40 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated. The 5.4 g of residue was purified through HPLC and final recrystallization from EtOAc/MeOH to give 1.7 g of product, m.p. 118-121° C (one third hydrate).

Anal. Calcd. for $C_{16}H_{17}N_3O_4S \cdot 1/3\ H_2O$:	C, 54.38; H, 5.04; N, 11.89
Found:	C, 54.09; H, 5.03; N, 12.02.

EXAMPLE30

2-[[(3,4-Difluorophenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using α-bromo-3,4-difluorotoluene, m.p. 147-149° C.

Anal. Calcd. for $C_{13}H_9F_2N_3S$:	C, 56.31; H, 3.27; N, 15.15
Found:	C, 56.00; H, 3.20; N, 14.96.

EXAMPLE31

2-[[(3,4-Difluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]-pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 170-173° C (dec.) (one tenth hydrate)

Anal. Calcd. for $C_{13}H_9F_2N_3OS \cdot 1/10\ H_2O$:	C, 52.91; H, 3.14; N, 14.24
Found:	C, 52.75; H, 3.02; N, 14.18.

EXAMPLE32

2-[[(Pentafluorophenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using α-bromo-2,3,4,5,6-pentafluorotoluene, m.p. 156-159° C.

Anal. Calcd. for $C_{13}H_6F_5N_3S$: C, 47.14; H, 1.83; N, 12.68
Found: C, 46.78; H, 1.52; N, 12.45.

EXAMPLE33

2-[[(Pentafluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]-pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 114-117° C (hemihydrate)

Anal. Calcd. for $C_{13}H_6F_5N_3OS \cdot 1/2\ H_2O$: C, 43.82; H, 1.98; N, 11.79
Found: C, 43.65; H, 1.79; N, 11.78.

EXAMPLE34

2-[[(3-Methylphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using α-chloro-m-xylene, m.p. 166-168° C.

Anal. Calcd. for $C_{14}H_{13}N_3S$: C, 65.85; H, 5.13; N, 16.46
Found: C, 65.64; H, 4.75; N, 16.37.

EXAMPLE35

2-[[(3-Methylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]-pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 175-177° C (dec.) ($\frac{1}{4}$ hydrate)

Anal. Calcd. for $C_{14}H_{13}N_3OS \cdot 1/4\ H_2O$: C, 60.96; H, 4.93; N, 15.23
Found: C, 60.93; H, 4.83; N, 15.11.

EXAMPLE36

2-[[(4-t-Butylphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 4-tert-butylbenzyl chloride, m.p. 207-208° C.

Anal. Calcd. for $C_{17}H_{19}N_3S$: C, 68.65; H, 6.44; N, 14.13
Found: C, 68.43; H, 6.34; N, 14.11.

EXAMPLE37

2-[[(4-t-Butylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 215-217° C (dec.).

Anal. Calcd. for $C_{17}H_{19}N_3OS$:	C, 65.15; H, 6.11; N, 13.40
Found:	C, 64.67; H, 6.20; N, 13.07.

EXAMPLE38

2-[(1H-Imidazo[4,5-c]pyridin-2-ylthio)methyl]benzonitrile

The synthesis of this compound proceeded in the same fashion as in Example 11 using α-bromo-o-tolunitrile, m.p. 200-202° C.

Anal. Calcd. for $C_{14}H_{10}N_4S$:	C, 63.14; H, 3.78; N, 21.04
Found:	C, 62.87; H, 3.63; N, 20.83.

EXAMPLE39

2-[[(1H-Imidazo[4,5-c]pyridin-2-yl)sulfinyl]methyl]benzonitrile

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 179-182° C.

Anal. Calcd. for $C_{14}H_{10}N_4OS$:	C, 59.56; H, 3.57; N, 19.84
Found:	C, 59.20; H, 3.38; N, 19.44.

EXAMPLE40

2-[[(2-Fluorophenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 2-fluorobenzyl chloride, m.p. 186-188° C.

Anal. Calcd. for $C_{13}H_{10}FN_3S$:	C, 60.21; H, 3.89; N, 16.20
Found:	C, 60.19; H, 3.76; N, 16.48.

EXAMPLE41

2-[[(2-Fluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 145-148° C (dec.) ($\frac{1}{4}$ hydrate)

Anal. Calcd. for $C_{13}H_{10}FN_3OS \cdot 1/4H_2O$:	C, 55.80; H, 3.78; N, 15.02
Found:	C, 55.77; H, 3.55; N, 14.94.

EXAMPLE42

2-[[(2-Methoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 2-methoxybenzyl chloride, m.p. 193-195° C.

Anal. Calcd. for $C_{14}H_{13}N_3OS$:	C, 61.97; H, 4.83; N, 15.49
Found:	C, 61.67; H, 5.00; N, 15.29.

EXAMPLE43

2-[[(2-Methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 209-211° C (dec.).

Anal. Calcd. for $C_{14}H_{13}N_3O_2S$:	C, 58.52; H, 4.56; N, 14.62
Found:	C, 58.20; H, 4.57; N, 14.41.

EXAMPLE44

2-[[(3,5-Dimethoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 3,5-dimethoxybenzyl chloride, m.p. 177-179° C.

Anal. Calcd. for $C_{24}H_{25}N_3O_4S$:	C, 63.85; H, 5.58; N, 9.31
Found:	C, 63.60; H, 5.32; N, 9.15.

EXAMPLE45

2-[[(3,5-Dimethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 207-210° C (dec.).

Anal. Calcd. for $C_{15}H_{15}N_3O_3S$:	C, 56.77; H, 4.76; N, 13.24
Found:	C, 56.53; H, 4.82; N, 12.89.

EXAMPLE46

2-[[(3-Phenoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 3-phenoxybenzyl chloride, m.p. 156-158° C.

Anal. Calcd. for $C_{19}H_{15}N_3OS$:	C, 68.45; H, 4.53; N, 12.60
Found:	C, 68.35; H, 4.44; N, 12.45.

EXAMPLE47

2-[[(3-Phenoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 210-212° C (dec.) (quarterhydrate)

Anal. Calcd. for $C_{19}H_{15}N_3O_2S \bullet 1/4\ H_2O$:	C, 64.48; H, 4.42: N, 11.87
Found:	C, 64.41; H, 4.18; N, 11.77.

EXAMPLE48

2-[[(3-Nitrophenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 3-nitrobenzyl chloride, m.p. 208-210° C.

Anal. Calcd. for $C_{13}H_{10}N_4O_2S$:	C, 54.53; H, 3.52; N, 19.57
Found:	C, 54.15; H, 3.70; N, 19.31.

EXAMPLE49

2-[[(3-Nitrophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 214-217° C (dec.) as the 0.15 dimethylformamide solvate.

Anal. Calcd. for $C_{13}H_{10}N_4O_3S \bullet 0.15$ DMF:	C, 51.56; H, 3.56; N, 18.56
Found:	C, 51.48; H, 3.50; N, 18.50.

EXAMPLE50

2-[[(4-Methoxy-3-methylphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 4-methoxy-3-methylbenzyl chloride, m.p. 158-159° C.

Anal. Calcd. for $C_{15}H_{15}N_3OS$:	C, 63.13; H, 5.30; N, 14.73
Found:	C, 62.95; H, 5.36; N, 14.67.

EXAMPLE51

2-[[(4-Methoxy-3-methylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 189-192° C (dec.).

Anal. Calcd. for $C_{15}H_{15}N_3O_2S$:	C, 59.78; H, 5.02; N, 13.94
Found:	C, 59.44; H, 4.70; N, 13.76.

EXAMPLE52

2-[[(3-Ethoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 11 using 3-ethoxybenzyl chloride, m.p. 158-161° C.

Anal. Calcd. for $C_{15}H_{15}N_3OS$:	C, 63.13; H, 5.30; N, 14.72
Found:	C, 62.98; H, 5.24; N, 14.47.

EXAMPLE53

2-[[(3-Ethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

The synthesis of this compound proceeded in the same fashion as in Example 10, m.p. 166-167° C (dec.) (one third hydrate).

Anal. Calcd. for $C_{15}H_{15}N_3O_2S \cdot 1/3\ H_2O$:	C, 58.61; H, 5.14; N, 13.67
Found:	C, 58.61; H, 4.89; N, 13.70.

EXAMPLE54

3-[[(1H-Imidazo[4,5-c]pyridin-2-yl)thio]methyl]phenol

To 20 mL of boron bromide in a round bottom flask was added in portions and with stirring 2.49 g of 2-[[3-methoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine (Example 2). The reaction flask was protected from moisture by a calcium chloride tube. Stirring was continued for 72 hours. The reaction mixture was added dropwise to 200 mL of methanol which was cooled in dry ice. The methanol solution was evaporated to one-half volume. The product which formed as a precipitate was collected on a filter and washed with acetone giving 1.07 g of white crystals, m.p. >300° C. (dihydrobromide salt)

Anal. Calcd. for $C_{13}H_{11}N_3OS \cdot 2HBr$: C, 27.25; H, 3.13; N, 10.02
C, 36.86; H, 3.03; N, 10.40

EXAMPLE55

N-[4-[(1H-Imidazo[4,5-c]pyridin-2-ylthio)methyl]phenyl]acetamide

The synthesis of this compound proceeded in the same fashion as in Example 11 using 4-acetamidobenzyl chloride, m.p. 231-234° C.

Anal. Calcd. for $C_{15}H_{14}N_4OS$: C, 60.38; H, 4.73; N, 18.78
Found: C, 60.28; H, 4.96; N, 18.42.

EXAMPLE56

N-[4-[(1H-Imidazo[4,5-c]pyridin-2-ylsulfinyl)methyl]phenyl]acetamide

The synthesis of this compound proceeded in the same fashion as in Example 12, m.p. 168-171° C (dec.) (one and one quarter hydrate).

Anal. Calcd. for $C_{15}H_{14}N_4O_2S \cdot 1.25\ H_2O$: C, 53.71; H, 4.52; N, 16.70
Found: C, 53.77; H, 4.63; N, 16.06.

EXAMPLE57

[S-(+)]-2-[[3-Methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

A slurry of 6.0 g (0.0262 mol) of (+)-(2R, 8aS) (camphorylsulfonyl) oxaziridine in 125 mL of methylene chloride was sonicated at room temperature until a clear solution was obtained. A solution of 7.11 g (0.0262 mol) of 2-[[3-(methoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine in 125 mL of ethanol was added to the oxaziridine solution. The reaction solution was sonicated for five days at 20° C, while running water through cooling coils. During the sonication process the reaction vessel was kept under a nitrogen atmosphere. The reaction mixture was subjected to HPLC. The fractions showing one spot corresponding to the desired sulfoxide were evaporated at room temperature. There was obtained 2.2 g of product $[\alpha]_D^{25} = +84.5°$. A chiral analytical HPLC column indicated the product was 81.3% (+) enantiomer and 18.7% (-) enantiomer, m.p. 185-188° C (dec.).

Anal. Calcd. for $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56; N, 14.62
Found: C, 58.14; H, 4.41; N, 14.51.

EXAMPLE58

[R-(-)1-2-[[(3-Methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine

Following the procedure of Example 57, the combined solutions of 5.16 g (0.019 mol) of 2-[[3-(methoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine in 220 mL of ethanol and 7.15 g (0.019 mol) of (-)-α,α-dichlorocamphorsulfonyloxaziridine (F. A. Davis, R. T. Reddy, and M. C. Weismiller, J. Am. Chem. Soc.,

111, 5964 (1989)) in 110 mL of methylene chloride were sonicated for 8 days at 20° C. The reaction mixture was subjected to HPLC. The fractions showing one spot corresponding to the desired sulfoxide were evaporated at room temperature. There was obtained 1.52 g of product as the ¼ hydrate $[\alpha]_D^{25}$ = -99.4°. A chiral analytical HPLC column inidcated the product was 85.4% (-) enantiomer and 14.6% (+) enantiomer, m.p. 175-178° C(dec.).

Anal. Calcd. for $C_{14}H_{13}N_3O_2S \bullet 1/4H_2O$: C, 57.62; H, 4.66; N, 14.40
Found: C, 57.69; H, 4.41; N, 14.30.

The useful osteoporotic activity of the compounds of formula (I) are demonstrated by standard pharmacological tests, for example, the test designated: Bone Resorption Assay: ^{45} Ca Release from Rat Limb Bones.

The purpose of this assay is to identify compounds that inhibit basal or stimulated bone resorption in culture.

The ability of 2-substituted-imidazo[4,5-c]pyridines to modify the process of bone resorption was evaluated essentially as described by L.G. Raisz, Bone resorption in tissue culture. Factors influencing the response to parathyroid hormone. (J. Clin. Invest. 44:103-116, 1965) and P.H. Stern et al, comparisons of fetal rat limb bones and neonatal mouse calvaria: Effects of parathyroid hormone and 1,25-dihydroxyvitamin D_3 (Calcif. Tissue Int. 35:172-176, 1983).

PROCEDURE:

Limb bone preparation. Timed pregnant Sprague-Dawley CD® rats (Charles River) are administered 100 μCi $^{45}CaCl_2$ (NEN calcium -45 NEZ-013) in 100 μLof 0.9% saline, subcutaneously, on day 18 of gestation. The rats are sacrificed the following day by CO_2 asphyxiation. The fetuses are removed and the right forelimbs excised and placed in a Petri dish containing ice cold explant medium consisting of modified BGJ_b-Fitton Jackson media (custom formulation, Gibco No. 78-0088) adjusted to pH 7.3 to which 10 mM TES is added. The modified BGJ_b media is obtained without salts, glucose or bicarbonate and is supplemented before use with 0.1 mM $MgCl_2$, 1.25 mM $CaCl_2$, 5.3 mM KCl, 0.7 mM $MgSO_4$, 130 mM NaCl, 1.0 mM NaH_2PO_4, 1 g/L glucose, 50 mg/L Na acetate and 100 U/mL penicillin G. The medium is sterilized by passage through a 0.2 μM filter (Nalge). Under a dissecting microscope, the bones are gently cleaned of adherent tissue and the cartilaginous ends removed. Incubation and drug treatment. The midshafts are placed, individually, on 3x3 mm squares of filter paper (Gelman GN-6 metricel filters; 0.45 μM pore size) which rest on stainless steel screens in wells of 24-well culture plates containing 0.5 mL of preincubation medium. The preincubation medium is brought to 37° C prior to transfer of bones. The preincubation medium consists of the modified BGJ_b medium (with salts and glucose as above), pH 7.3, containing 29 mM $NaHCO_3$. After incubation for 18-24 hours at 37° C in 5% CO_2, the bones are transferred on their screen/filter paper supports to new plates containing, in a total volume of 0.5 mL/well at 37° C, the test compound diluted in preincubation medium supplemented with 15% heat inactivated horse serum (Gibco No. 230-6050), pH 7.3, with or without a bone resorption stimulating agent (e.g. parathyroid hormone [PTH] or interleukin-1 [IL-1]). For compounds that require nonaqueous solvents, dilutions are made from the appropriate stock solution with medium. In these instances, basal and bone resorption stimulated controls exposed to an equivalent concentration of the vehicle are included. An additional group of bones that have been subjected to boiling for 1 hour (kill control) are used to establish background, non cell mediated, exchange of ^{45}Ca. The right ulna and radius from each fetus are used. Both bones are subjected to the same treatment and each treatment group consists of bones from 4 or more fetuses. Treatments are randomly assigned using a preclinical statistics program (PS-ALLOC). After a 48 hour incubation at 37° C in 5% CO_2, the bones are removed from the medium and extracted in 0.5 mL of 0.1 N HCl for 1 or more days. Duplicate 150 μL aliquots of the incubation medium and the bone extract are analyzed for ^{45}Ca radioactivity in 5 mL of liquid scintillation cocktail.

CALCULATIONS:

The percentage of bone ^{45}Ca released into the medium is determined as follows:

$$\frac{^{45}Ca\ CPM\ in\ medium}{^{45}Ca\ CPM\ in\ medium + ^{45}Ca\ CPM\ in\ bone} \times 100$$

Results are normally expressed as the ratio of the percent ^{45}Ca release of the experimental group versus the appropriate vehicle control.

The results of this assay are set forth in TABLE 1 under the heading PTH Induced.

The useful osteoporotic activity of the compounds of formula (I) are further demonstrated by the test designated: Basal Bone Resorption Assay: ^{45}Ca Release from Rat Limb Bones.

The purpose of this assay is to test stimulators and inhibitors of bone resorption in vitro. The release of ^{45}Ca from in vitro labeled murine bone explants into the culture media is taken as an index of bone resorption.

Bone labelling procedure. Rat pups are labelled in vitro by injecting pregnant dams (18 days) with 100 μCi of ^{45}Ca.

Explant preparation. Two days after the initiation of labelling, the dam is anesthetized with halothane and killed by cervical dislocation. The pups are ablated and quickly decapitated. The calvaria (frontal and parietal bones), forelimbs (containing radii and ulnae), and hind limbs (tibiae) are removed and placed in control media in a petri dish. Bones are debrided of soft tissue by a combination of blunt dissection, and gentle rolling on bibulous paper, taking care not to disturb the periosteum. Cartilaginous ends are cut off long bones. Calvaria are cut in half along midline suture. Bones are separated into 3 categories: calvaria halves, Tibiae and ulnae/radii. Groups of eight (per bone group) are randomly placed in 24-well culture plates containing 0.5 mL of control media. Cultures are maintained at 37° C in a humidified incubator of 95% air: 5%CO_2.

These bones are incubated for 24 hours, media is aspirated from the bones and replaced with fresh media containing test substances. Each bone group has a control group of 8 and a dead bone group of 8. The devitalized cultures are obtained by heating the bones in medium at 55° C for 60 minutes. The bones are incubated at 37° C for an additional 72 hours. At the end of this period a 100 microliter aliquot of media is removed and placed in a scintillation vial. Ten mL of Aquasol is added, the ^{45}Ca is quantified in a scintillation spectrometer. Bones are rinsed in saline, placed in a scintillation vial, hydrolyzed overnight in 0.75 mL 6N HCl at room temperature. The hydrolyzed bone solution is neutralized by the addition of 2.25 mL of 2N NaOH, followed by 10 mL of Aquasol, the ^{45}Ca content is determined by scintillation spectrometry.

Analysis: ^{45}Ca release into culture medium from the 24-96 hour period is individually compared to ^{45}Ca release in control cultures and to devitalized bone via Dunnett's test. Results are expressed in TABLE 1 under the heading Basal.

The useful osteoporotic activity of the compounds of formula (I) are further demonstrated by the test designated: Denervation Induced Osteopenia in Rats.

The purpose of this assay is to evaluate the effect, in rats, of agents on the reduction in bone mass (osteopenia) induced by immobilization resulting from surgical severance (denervation) of the sciatic nerve.

Female, Sprague Dawley CD® rats, ovariectomized or intact, weighing 225 to 250 g, obtained from Charles River are used.

The animals are housed in plastic cages (4 or 5 rats/cage) with food (rat purina 500 chow) and water ad libitum; 14/10 day/night cycle.

After one week of in-house acclimatization, the animals are randomly divided into groups of 6 to 10 rats/group. Each rat is weighed, anesthetized with an intraperitoneal administration of 100 mg/kg ketamine (Bristol Laboratories, Syracuse, NY) and 0.75 mg/kg Acepromazine (Aveco, Ft. Dodge IA). The left hind limb is shaved and denervated by making a lateral incision parallel to the femur and by surgically removing half of a centimeter of the sciatic nerve adjacent to caudofemoralis and adductor brevis muscles. The incision is closed with wound clips. After surgery, the rats are housed in cages with absorbent bedding to minimize additional trauma to the immobilized limb. A 24 hour post-surgery recovery period is allowed before the initiation of the drug treatment.

The concentration of the drug stock is calculated to be delivered in a volume of 0.1 mL/100 gram body weight. The drug solution or a uniform suspension is prepared in 1% Tween 80 in normal saline. The drugs are administered via oral or parenteral routes daily (five times a week) for four weeks.

A sequential triple labeling of mineralized tissue is employed to determine the osseous changes (especially the bone formation) and the mineralization rates. Each animal is administered 90 mg/kg Xylenol

orange (Fisher Scientific Company), S.C., 15 mg/kg Calcein (Sigma Chemical Company), S.C. and 15 mg/kg Demeclocycline (Sigma Chemical Company), i.p., approximately 21 days, 10 days and 2 days prior to the termination of the study, respectively.

At the end of the fourth week, each rat is weighed, anesthetized with an intraperitoneal administration of 100 mg/kg ketamine with 0.75 mg/kg Acepromazine and approximately 4 mL of blood collected via cardiac puncture. The anesthetized rats are euthanized by exposure to carbon dioxide. The femora and tibiae from both limbs are dissected free of soft tissue.

(i) Femora are ashed at ~1100° C for 16 hours using a muffle furnace. - (ii) Proximal tibia are fixed, dehydrated and embedded undecalcified in a methyl methacrylate-glycol methacrylate mixture. Longitudinal tissue sections (10 microns) are prepared on a Polycut S microtome (Reichert). Staining is performed on free-floating sections using a modified Goldner's stain, which are then mounted and coverslipped.

Cancellous bone content in the proximal tibia is quantified (as two dimensional bone mineral area [B.Ar]) with an image analysis processing device (software developed by Drexel University).

The areas of the tibia selected for cancellous bone content evaluation are the primary and secondary spongiosa. To select and standardize this area for evaluation, the epiphyseal growth plate-metaphyseal junction is oriented parallel to the abscissa of the digitizing screen. Bone elements 1.7 mm (secondary spongiosa) and 0.2 mm (primary spongiosa) from the growth plate and equidistant from the flanking cortical elements are then quantified as described above. The total area evaluated is 2.30 mm wide and 1.45 mm deep, constituting a 3.34 mm^2 area.

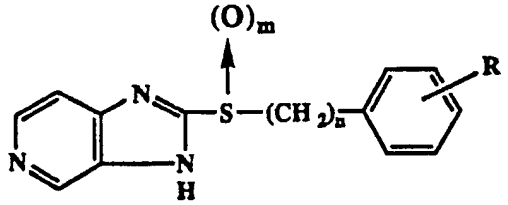
Body weight, femur mass (dried or ashed) and trabecular (cancellous) bone mineral area (B.Ar) are determined.

The difference (both absolute and percent change) in femur mass and bone mineral area between intact (control) and denervated limbs of a treatment group are compared with that for the vehicle group using a one-way analysis of variance with Dunnett's test, or other multiple comparison methods.

The results are reported in Table I and II under the heading In Vivo.

TABLE I

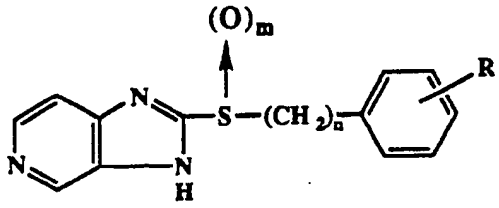
Imidazo[4,5-c]pyridine Sulfoxide and Sulfone Analogs



Example	n	R	m	Inhibition of Bone Resorption		
				PTH Induced	Basal	In Vivo
3	1	3-methoxy	1	Active IC_{50}=49 µM	Active 10 µg/mL	Active
4	1	3-methoxy	2	Active 10 µg/mL	Marginal 10 µg/mL	Inactive
6	1	3,4-dichloro	1	Active 10 µg/mL	Active 10 µg/mL	NT
8	1	3-trifluoromethyl	1	Active 10 µg/mL	Inactive	NT
10	1	2-chloro-6-fluoro	1	Active 10 µg/mL	Active 10 µg/mL	Inactive
12	1	hydrogen	1	Active 10 µg/mL	Active 10 µg/mL	Inactive
14	2	hydrogen	1	Active 10 µg/mL	Active 10 µg/mL	NT
17	2	3-methoxy	1	Active 10 µg/mL	Inactive 10 µg/mL	Borderline
19	1	2,4,6-trimethyl	1	Active 10 µg/mL	Active 10 µg/mL	Inactive
21	1	2-fluoro-4-bromo	1	Active 10 µg/mL	Active 10 µg/mL	Inactive
23	1	3-benzyloxy	1	Active 10 µg/mL	Active 10 µg/mL	Inactive
25	1	2-chloro-4,5-methylenedioxy	1	Active 10 µg/mL	Active 10 µg/mL	Inactive
27	1	4-methoxy	1	Active 10 µg/mL	NT	Inactive
29	1	3,4,5-trimethoxy	1	Inactive	NT	Inactive
31	1	3,4-difluoro	1	Active 10 µg/mL	Active 10 µg/mL	Inactive
33	1	pentafluoro	1	NT	NT	NT
35	1	3-methyl	1	NT	NT	NT
37	1	4-tert-butyl	1	NT	NT	NT
39	1	2-cyano	1	Active 10 µg/mL	NT	Inactive
41	1	2-fluoro	1	Active 10 µg/mL	NT	Inactive

TABLE I (Cont.)

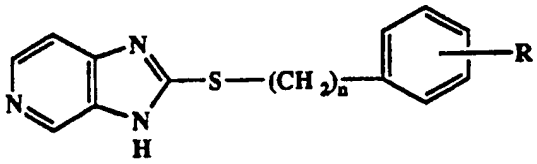
Imidazo[4,5-c]pyridine Sulfoxide and Sulfone Analogs



Example	n	R	m	Inhibition of Bone Resorption		
				PTH Induced	Basal	In Vivo
43	1	2-methoxy	1	Active 10 µg/mL	NT	NT
45	1	3,5-dimethoxy	1	Active 10 µg/mL	NT	Inactive
47	1	3-phenoxy	1	Active 10 µg/mL	NT	Inactive
49	1	3-nitro	1	NT	NT	Inactive
51	1	4-methoxy-3-methyl	1	NT	NT	Inactive
53	1	3-ethoxy	1	Active 10 µg/mL	NT	NT
56	1	3-aminoacetyl	1	NT	NT	NT
57	1	S-(+)-3-methoxy	1	Active	NT	NT
58	1	R-(-)-3-methoxy	1	Active	NT	NT

TABLE II

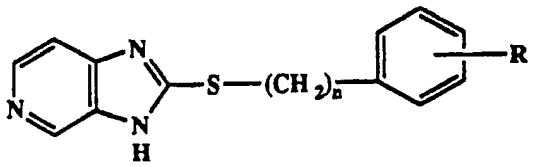
Imidazo[4,5-c]pyridine Sulfide Analogs



Example	n	R	Inhibition of Bone Resorption		
			PTH Induced 10 µg/mL	Basal 10 µg/mL	In Vivo 25 mg/kg
2	1	3-methoxy	Inactive	Inactive	Active (i.p.)
5	1	3,4-dichloro	NT	Inactive	NT
7	1	3-trifluoromethyl	NT	Active	NT
9	1	2-chloro-6-fluoro	Inactive	Inactive	NT
11	1	hydrogen	NT	Inactive	NT
13	2	hydrogen	Inactive	Inactive	NT
16	2	3-methoxy	Inactive	NT	Inactive (p.o.)
18	1	2,4,6-trimethyl	NT	NT	NT
20	1	2-fluoro-4-bromo	Active	Inactive	NT
22	1	3-benzyloxy	Active	Inactive	NT
24	1	2-chloro-4,5-methylenedioxy	Active	NT	NT
26	1	4-methoxy	Active	Inactive	Inactive (p.o.)
28	1	3,4,5-trimethoxy	NT	NT	NT
30	1	3,4-difluoro	Inactive	Inactive	Inactive (p.o.)
32	1	pentafluoro	Inactive	Inactive	Inactive (p.o.)
34	1	3-methyl	NT	NT	NT
36	1	4-tert-butyl	NT	NT	NT

TABLE II (Cont.)

Imidazo[4,5-c]pyridine Sulfide Analogs



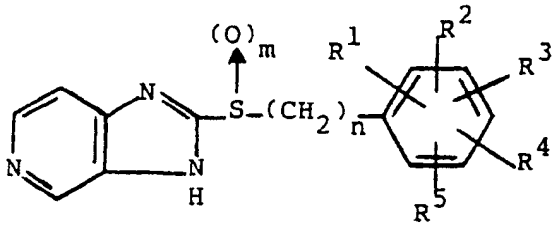
Example	n	R	Inhibition of Bone Resorption		
			PTH Induced 10 µg/mL	Basal 10 µg/mL	In Vivo 25 mg/kg
38	1	2-cyano	Inactive	NT	Inactive
40	1	2-fluoro	Active	NT	Inactive
42	1	2-methoxy	Active	NT	NT
44	1	3,5-dimethoxy	Active	NT	Inactive
46	1	3-phenoxy	Inactive	NT	Inactive
48	1	3-nitro	NT	NT	Inactive
50	1	4-methoxy-3-methyl	NT	NT	Inactive
52	1	3-ethoxy	Inactive	NT	Inactive
54	1	3-hydroxy	Inactive	NT	Inactive
55	1	3-acetamido	NT	NT	NT

Bone is degraded during the process of bone resorption and this leads to the subsequent development of osteoporosis. The present invention provides a method for the treatment of a host animal in order to modify the balance between the rate of bone resorption and the rate of bone deposition in said host animal whereby the ratio of said rate of bone resorption to said rate of bone deposition is reduced, comprising administering to said host animal an amount, sufficient to modify said balance and reduce said ratio, of 2-substituted-imidazo[4,5-c]pyridines. 2-Substituted-imidazo[4,5-c]pyridines would be administered to humans at a daily dose of 200 mg to 1200 mg.

The administration of 2-substituted-imidazo[4,5-c]pyridines in accordance with this invention can be supplemental to other regimens for the treatment of osteoporosis or periodontitis. For example, the administration of 2-substituted-imidazo[4,5-c]pyridines can be supplemental to the 600 mg to 1200 mg daily intake of calcium as calcium phosphate or calcium carbonate. Also, the administration of 2-substituted-imidazo[4,5-c]pyridines can be supplemental to estrogen replacement therapy such as 0.625 mg daily of conjugated equine estrogen.

Claims

1. A compound of formula (I)



or tautomer thereof, wherein R^1, R^2, R^3, R^4 and R^5 are independently selected from hydrogen, lower alkyl containing 1 to 6 carbon atoms, hydroxy, lower alkyloxy containing 1 to 6 carbon atoms, halogen, trifluoromethyl, trifluoromethoxy, nitro, cyano, phenoxy, benzyloxy, acetamido, $-S(O)_p-CH_3$ or any two adjacent groups are joined to form methylenedioxy; m is 0 to 2; n is 1 to 3; p is 0 to 2, or a pharmaceutically acceptable salt or hydrate thereof.

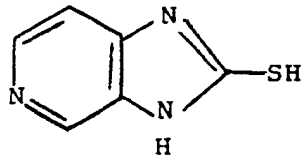
2. A compound as claimed in Claim 1 wherein R^1, R^2, R^3, R^4 and R^5 are independently selected from hydrogen, hydroxy, methoxy, fluorine, bromine, chlorine, methyl, trifluoromethyl, benzyloxy or any two adjacent groups are joined to form methylenedioxy; m is 0 to 2; n is 1 or 2, or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in Claim 1 which is one of the following
2-[[(3-Methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Methoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Methoxyphenyl)methyl]sulfonyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3,4-Dichlorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[[[3-Trifluoromethyl)phenyl]methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(2-Chloro-6-fluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(Phenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[(2-Phenylethyl)sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Methoxyphenyl)ethyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(2,4,6-Trimethylphenyl)methyl]sulfinyl]-1 H-imidazo[4,5-c]pyridine;
2-[[(4-Bromo-2-fluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[[3-Phenylmethoxy)phenyl]methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(6-Chloro-1,3-benzodioxol-5-yl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(4-Methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3,4,5-Trimethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3,4-Difluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(Pentafluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Methylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(4-t-Butylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(1H-Imidazo[4,5-c]pyridin-2-yl)sulfinyl]methyl]benzonitrile;
2-[[(2-Fluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(2-Methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3,5-Dimethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Phenoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Nitrophenyl)methyl]sulfinyl]-1H-imadazo[4,5-c]pyridine;
2-[[(4-Methoxy-3-methylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Ethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
N-[4-[(1H-Imidazo[4,5-c]pyridin-2-ylsulfinyl)methyl]phenyl]acetamide;
[S-(+)]-2-[(3-methoxyphenyl)methyl)sulfinyl]-1H-imidazo[4,5-c]pyridine;
or
[R-(-)]-2-[[(3-methoxyphenyl)methyl] sulfinyl]-1H-imidazo[4,5-c]pyridine; or a pharmaceutically acceptable salt thereof.

4. A compound as claimed in Claim 1 which is 3-[[(1H-Imidazo[4,5-c]pyridin-2-yl)sulfinyl]methyl]phenol or a pharmaceutically acceptable salt thereof.

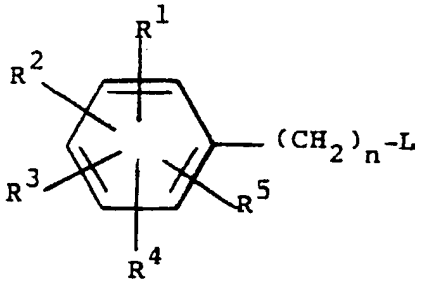
5. A compound as claimed in any one of Claims 1 to 4 when in the form of a salt of an acid selected from hydrochloric, hydrobromic, phosphoric, sulfuric, sulfamic, nitric, methylsulfonic, maleic, fumaric, and naphthalenesulfonic acid.

6. A process for preparing a compound of formula I or tautomer thereof as claimed in Claim 1 which comprises one of the following:
a) reacting a compound of formula



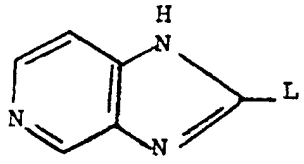
(II)

or tautomer thereof, or an alkali metal salt thereof e.g sodium, potassium or lithium salt, with a compound of formula



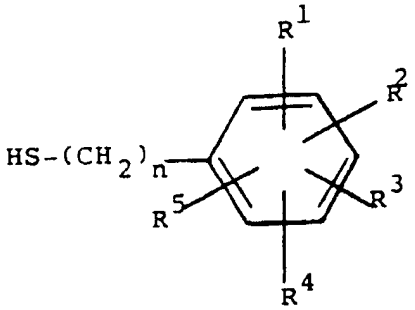
(III)

wherein n, R^1, R^2, R^3, R^4 and R^5 are as defined in Claim 1 and L is a leaving group to give a compound of formula I or tautomer thereof wherein m is zero, or
b) reacting a compound of formula



(IV)

or tautomer thereof, wherein L is a leaving group as described above with a compound of formula



(V)

or an alkali metal salt thereof wherein n, R^1, R^2, R^3, R^4 and R^5 are as defined in Claim 1 to give a

compound of formula I or a tautomer thereof wherein m is zero, or
c) oxidising a compound of formula I or a tautomer thereof to give a corresponding compound of formula I or tautomer thereof wherein m is 1 or 2, or
d) dealkylating a compound of formula I or tautomer thereof wherein any one of R^1, R^2, R^3, R^4 and R^5 is lower alkyloxy and m is 0 or 2 to give a compound of formula I or tautomer thereof wherein any one of R^1, R^2, R^3, R^4, and R^5 is hydroxy, or
e) acidifying a basic compound of formula I or tautomer thereof to give an acid addition salt or neutralizing an acid addition salt to give the free base of formula I or tautomer thereof.

7. A process a) or b) as claimed in Claim 6 wherein L is p-tosyloxy, chlorine, bromine or iodine.

8. A process a) or b) as claimed in Claim 6 or Claim 36 wherein the alkali metal salt is the sodium salt.

9. A process c) as claimed in Claim 6 wherein the oxidising agent is an optically active sulfonyl oxaziridine.

10. A compound of formula I or a tautomer or a pharmaceutically acceptable salt thereof as claimed in Claims 1 to 5 for use as an antiosteoporotic agent.

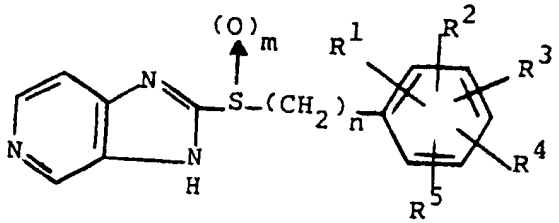
11. A pharmaceutical composition comprising a compound of formula I or tautomer or a pharmaceutically acceptable salt thereof as claimed in any one of Claims 1 to 5 and a pharmaceutically acceptable carrier.

12. Use of a compound of formula I or tautomer thereof or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of osteoporosis.

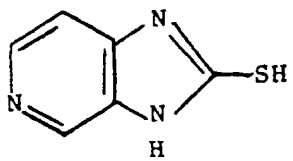
CLAIMS FOR THE FOLLOWING CONTRACTING STATES: GREECE AND SPAIN

1. A process for preparing a compound of formula

(I)



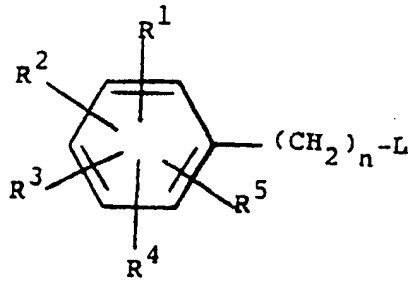
or tautomer thereof, wherein R^1, R^2, R^3, R^4 and R^5 are independently selected from hydrogen, lower alkyl containing 1 to 6 carbon atoms, hydroxy, lower alkyloxy containing 1 to 6 carbon atoms, halogen, trifluoromethyl, trifluoromethoxy, nitro, cyano, phenoxy, benzyloxy, acetamido, $-S(O)_p-CH_3$ or any two adjacent groups are joined to form methylenedioxy; m is 0 to 2; n is 1 to 3; p is 0 to 2, or a pharmaceutically acceptable salt or hydrate thereof, which comprises one of the following:
a) reacting a compound of formula



(II)

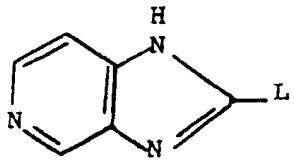
or tautomer thereof, or an alkali metal salt thereof e.g sodium, potassium or lithium salt, with a

compound of formula



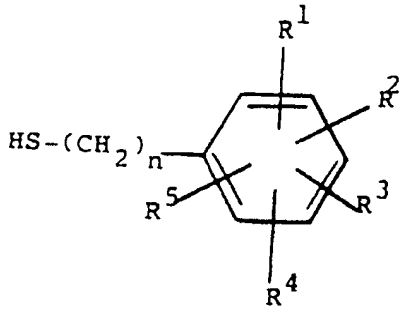
(III)

wherein n, R^1, R^2, R^3 R^4 and R^5 are as defined above and L is a leaving group e.g a halogen such as chlorine, bromine or iodine or an organic sulphonyloxy group such as aryl or alkyl-sulphonyloxy, e.g tosyloxy to give a compound of formula I or tautomer thereof wherein m is zero, or
b) reacting a compound of formula



(IV)

or tautomer thereof, wherein L is a leaving group as described above with a compound of formula



(V)

or an alkali metal salt thereof wherein n, R^1, R^2, R^3, R^4 and R^5 are as defined in above to give a compound of formula I or a tautomer thereof wherein m is zero, or
c) oxidising a compound of formula I or a tautomer thereof to give a corresponding compound of formula I or tautomer thereof wherein m is 1 or 2, or d) dealkylating a compound of formula I or tautomer thereof wherein any one of R^1, R^2, R^3, R^4 and R^5 is lower alkyloxy and m is 0 or 2 to give a compound of formula I or tautomer thereof wherein any one of R^1, R^2, R^3, R^4 and R^5 is hydroxy, or
e) acidifying a basic compound of formula I or tautomer thereof to give an acid addition salt or neutralizing an acid addition salt to give the free base of formula I or tautomer thereof.

2. A process a) or b) as claimed in Claim 1 wherein L is p-tosyloxy, chlorine, bromine or iodine.

3. A process a) or b) as claimed in Claim 1 or Claim 2 wherein the alkali metal salt is the sodium salt.

4. A process c) as claimed in Claim 1 wherein the oxidising agent is an optically active sulfonyl oxaziridine.

5. A process as claimed in Claim 1 in which R^1, R^2, R^3, R^4 and R^5 in the product are independently

selected from hydrogen, hydroxy, methoxy, fluorine, bromine, chlorine, methyl, trifluoromethyl, benzyloxy or any two adjacent groups are joined to form methylenedioxy; m is 0 to 2; n is 1 or 2, or a pharmaceutically acceptable salt thereof.

6. A process as claimed in any one of Claims 1 to 5 in which the product is one of the following: 2-[[(3-Methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine; 2-[[(3-Methoxyphenyl)methyl]thio]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Methoxyphenyl)methyl]sulfonyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3,4-Dichlorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[[[3-Trifluoromethyl)phenyl]methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(2-Chloro-6-fluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(Phenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[(2-Phenylethyl)sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Methoxyphenyl)ethyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(2,4,6-Trimethylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(4-Bromo-2-fluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[[3-Phenylmethoxy)phenyl]methyl]sulfinyl]--1H-imidazo[4,5-c]pyridine;
2-[[(6-Chloro-1,3-benzodioxol-5-yl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(4-Methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3,4,5-Trimethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3,4-Difluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(Pentafluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Methylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(4-t-Butylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(1H-Imidazo[4,5-c]pyridin-2-yl)sulfinyl]methyl]benzonitrile;
2-[[(2-Fluorophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(2-Methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3,5-Dimethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Phenoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Nitrophenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(4-Methoxy-3-methylphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
2-[[(3-Ethoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
N-[4-[(1H-Imidazo[4,5-c]pyridin-2-ylsulfinyl)methyl]phenyl]acetamide;
[S-(+)]-2-[[(3-methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
[R-(-)]-2-[[(3-methoxyphenyl)methyl]sulfinyl]-1H-imidazo[4,5-c]pyridine;
or
3-[[(1H-imidazo[4,5-c]pyridine-2-yl)]sulfinyl]methyl]phenol; or a pharmaceutically acceptable salt thereof.

7. A process for preparing a pharmaceutical composition which comprises mixing a compound of formula I or tautomer or a pharmaceutically acceptable salt thereof as defined in any one of Claims 1 to 6 with a pharmaceutically acceptable carrier.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT

EP 90313945.9

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	WO - A1 - 89/03 830 (AKTIEBOLAGET HÄSSLE) * Page 5, lines 1-13, formula-1 * --	1,10-12	C 07 D 471/04 A 61 K 31/44 //(C 07 D 471/04 C 07 D 235:00 C 07 D 221:00)
A	US - A - 4 880 815 (UCHIDA) * Claim 1; column 11, reaction formula-7; columns 12-13, reaction formula-8 * --	1,6	
A	EP - A1 - 0 234 690 (NIPPON) * Claims 1,6,17 * ----	1,6,11	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 D 471/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	05-02-1991	ONDER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)